Gadolinium-Based Contrast Agents (GBCAs) and the NSF Risk:

Regulatory Update

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Presentation Outline

- Introduction to Gadolinium-Based Contrast Agents (GBCAs)
- Nephrogenic Systemic Fibrosis (NSF)
- 2007 Initial Regulatory Response
- 2009 Advisory Committee
- 2010 Labeling Changes
- Consideration of a New GBCA

GBCA Background

- **GBCAs improve diagnostic capabilities of MRI**
- **Mechanism – paramagnetic properties of Gadolinium**
- **Neuro imaging and organ systems**
- **Most have renal excretion – prolonged in renal failure**

FDA-approved GBCAs

GBCA	Approval Date	Indication	Chemical Structure, Charge
Magnevist (Gadopentate)	**1988**	**CNS/ body**	**Chain, ionic**
Prohance (Gadoteridol)	**1992**	**CNS**	**Macrocyclic**
Omniscan (Gadodiamide)	**1993**	**CNS/ body**	**Chain, non ionic**
Optimark (Gadoversetamide)	**1993**	**CNS/ liver**	**Chain, non ionic**
Multihance (Gadobenate)	**2004**	**CNS**	**Chain, ionic**
Eovist (Gadoxetate)	**2008**	**Liver**	**Chain, ionic**
Ablavar (Gadofosveset)	**2008**	**MRA Aortoiliac**	**Chain, ionic**

Adverse Events (AEs) with GBCAs

- Overall incidence of AEs <3%
- Most common AEs: headache, nausea, emesis, injection site reactions
- True anaphylactoid reactions and serious AEs are rare but are reported for each GBCA
- Cautious use with h/o asthma, allergies

Nephrogenic Systemic Fibrosis (NSF)

- **1997-2001: described among patients with renal failure**
- **2006: associated with GBCA**
- **Scleroderma like but spares face and lacks serological markers**
- **Potentially lethal – respiratory failure**
- **No known treatment or cure**
- **Many skin lesions – mimic NSF**

Scope of Renal Insufficiency

US Renal Data Service 2008

Stage	Description	GFR (ml/min/1.73m^2)	Population
1	normal	≥90	~20 million
2	mild	60-90	
3	moderate	30-59	7.5 million
4	**severe**	**15-29**	**400,000**
5	**renal replacement**	**<15**	**300,000**

2007 Safety Labeling Change – Minimize the Risk!

- **Class labeling – risk with all GBCAs**
- **Available data did not allow for determination of differential risk (200 reports)**
- **Boxed warning – about use in:**
  - **Acute/chronic severe renal failure**
  - **Acute renal failure + liver ailments**
- **Post-marketing – Omniscan, Optimark, Magnevist – most reports**

2007 Warning Section

- Postmarketing reports have identified the development of NSF following single and multiple administrations of gadolinium-based contrast agents.
- These reports have not always identified a specific agent.
- **Where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan™), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK®).**

2007 – 2009 Advances in NSF Understanding

- **Stability constants - laboratory investigations of GBCA physicochemical properties – release of free Gadolinium**
- **NSF animal model attempted**
- **GBCA clinical usage data**
- **Accumulated post marketing reports**

2007 – 2009 New Data: *Pre-Clinical*

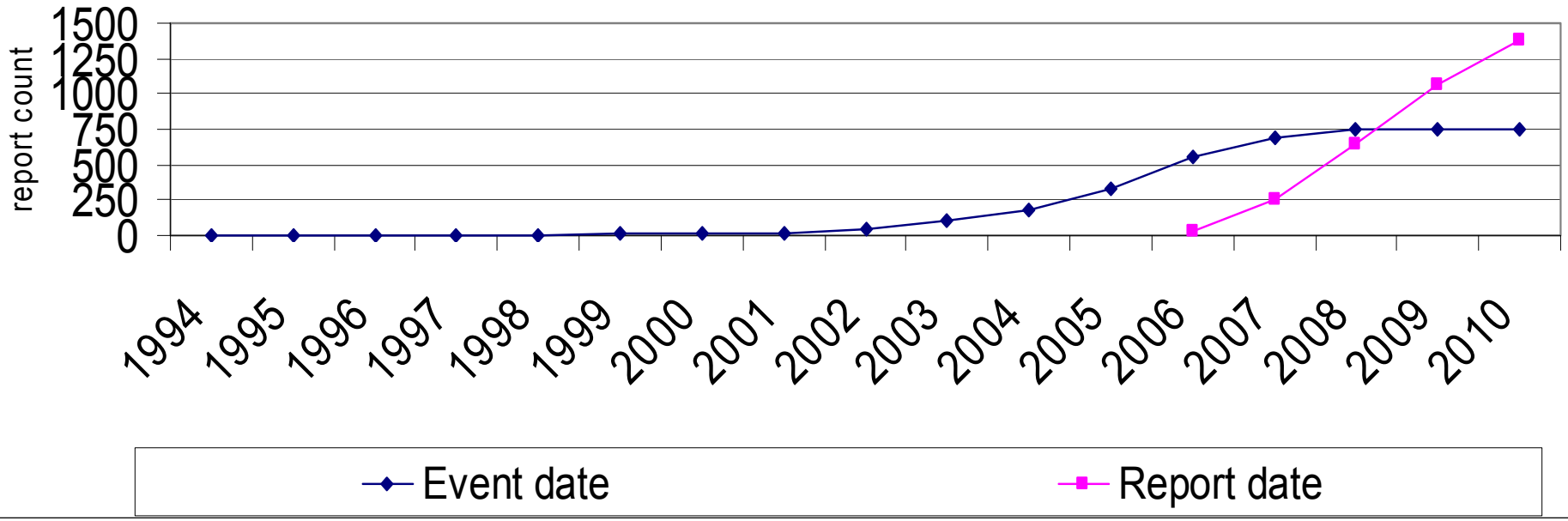
- **Transmetallation theory:**
  - **Liberation of free gadolinium → NSF**
  - **Low constants: GBCAs tend to liberate**
  - **High constants: tend to retain**
- **Gadolinium deposition in experimental animals with GBCAs that liberate Gadolinium**
- **Gadolinium triggers an immunologic cascade leading to fibrosis**

2007-09 New Data: *Clinical*

- **Postmarketing data reported to FDA**
  - **Many reports (>1200), but…**
    - **No event date**
    - **Specific GBCA not listed**
    - ***Confounded (multiple GBCAs)***
- **Coincident decrease in new NSF cases with screening and avoidance of high risk GBCAs**

AERS Reports

Cumulative, domestic reports of NSF in association with GBCAs for all reports to date (n=1,381) and the subset with event date (n=786).
AERS database: April 2010.



AERS NSF Reports (2009)

GBCA	Domestic Single-agent NSF Reports in AERS
Omniscan	382
Magnevist	195
Optimark	35
Prohance	0 (1 Foreign Report)
Multihance	1
Eovist	0
Ablavar	0

2009 Advisory Committee

- **Differential NSF risk exists**
- **Risk is consistent with data from multiple sources & transmetallation theory**
- **Higher Risk → Contraindicated: Omniscan, Optimark & (Magnevist) in severe renal failure/ acute kidney injury**
- **Lower Risk → Warning: Multihance, Prohance, Ablavar & Eovist**

Setting the NSF Safety Stage

- Consider the chemical structure
- Consider the limitations of the physico-chemical measures such as the various stability constants
- Consider the details of the NSF reports
- Consider which NSF risk category is appropriate

Back Up Slide

2010 Label – Higher Risk GBCA

NSF:

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.

- **Do not administer OMNISCAN to patients with:**
  - **chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or**
  - **acute kidney injury (4).**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g., age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.2).**

Gadobutrol Injection

Efficacy, Safety, NSF

Barbara Stinson, DO
Medical Officer
Division of Medical Imaging Products
Office of New Drugs
FDA/CDER
Gadobutrol AC, January 21, 2011

5 Marketed GBCAs With CNS Indication

Trade Name	Molar Strength	Dose (mmol/kg)	
		Adults	Pediatric
Magnevist	0.5	0.1	0.1
Prohance	0.5	0.1 (optional 2nd dose 0.2)	0.1
Omniscan	0.5	0.1	0.1 (0.05 kidney)
Optimark	0.5	0.1	N/A
Multihance	0.5	0.1	0.1
Gadovist	1.0	0.1	0.1

- Same dose
- 2x molar strength

½ the volume for Gadovist

Unique Gadobutrol Molar Strength Poses Risk for Overdosage

- Same dose
- 2x molar strength

½ the volume for Gadobutrol

Potential for Gadobutrol overdosage

Today's AC

- **Phase 3 data appear to support efficacy claim.**

FOCUS:

- **Gadobutrol's NSF risk in the context of recent NSF class labeling changes**
- **Implications of the potential for Gadobutrol overdosage on its NSF risk**

Discussion Topics

1. **Are data supportive of Gadobutrol approval?**

2. **Can FDA classify Gadobutrol as a GBCA with "lower" risk for NSF?**

3. **Discuss how to minimize risk for Gadobutrol medication errors that may lead to overdosage.**

Outline

- **Proposed indication and Phase 3 efficacy summary**
- **Safety summary**
- **Proposed methods to minimize risk of overdosage (and thus NSF risk)**

Proposed Gadobutrol Indication

- **intravenous use in diagnostic MRI**
- **to detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity (CNS)**

<u>Intended population:</u> Adults and children <u>≥</u>2 years with known or suspected CNS disease.

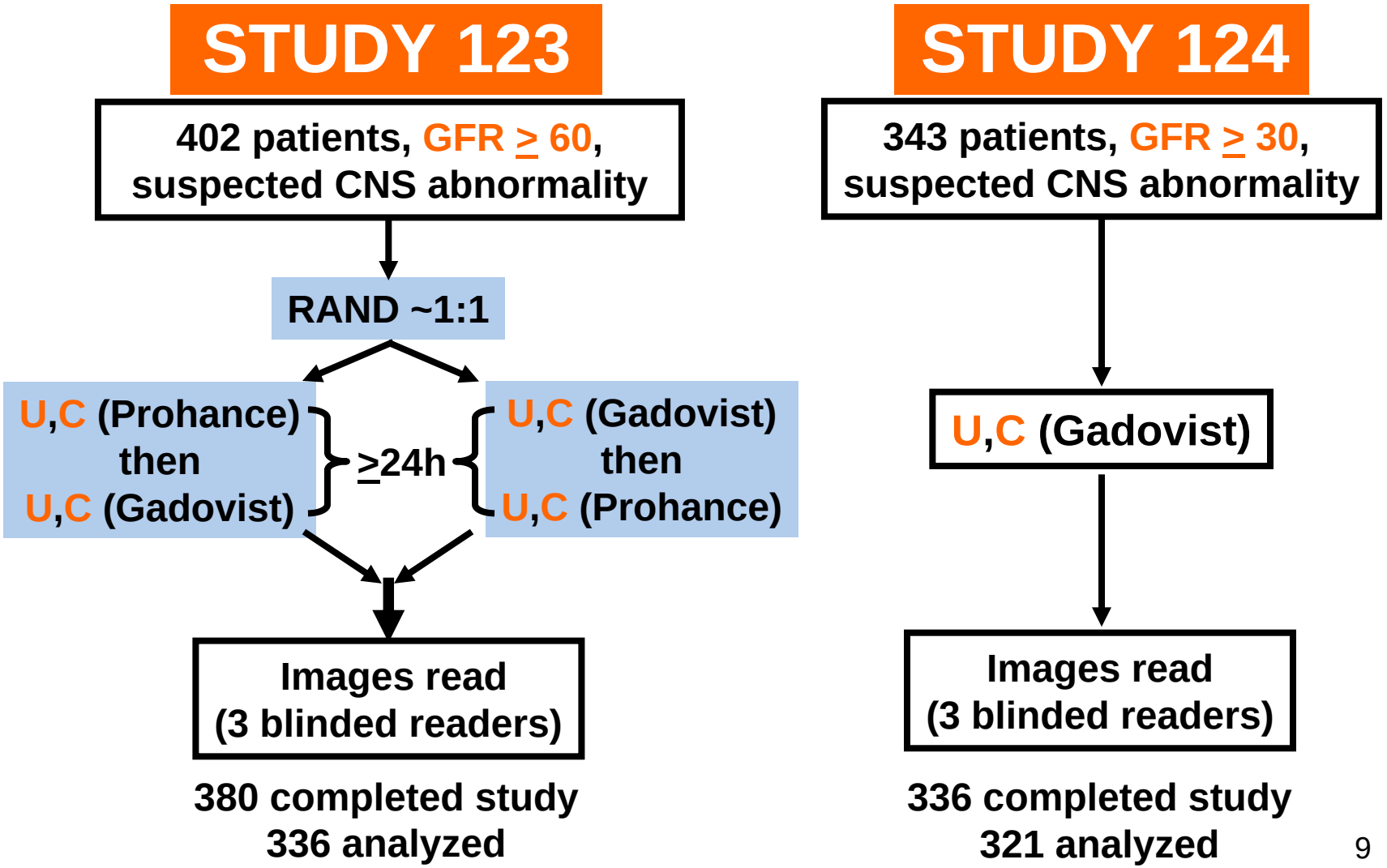
5 GBCAs With CNS Indication -- Phase 3 Study Designs --

- **Assessed structure "visualization" using blinded readers**

Contrasted MRI (C) vs Uncontrasted MRI (U)	or	paired C + U vs U

- **Gadobutrol: compared C + U vs U for detection, localization, and depiction of *intrinsic properties* of CNS lesions**

Gadobutrol Phase 3 Studies



Primary Endpoints Analyses
-- Study 123, 124 --

Compared "paired" (U + C) to U for:

- **Contrast enhancement**
- **Border delineation**
- **Internal morphology**

Average across readers, Paired t-test, 1-sided 0.025 CI

(superiority)

- **Number of lesions**

Average across readers, Noninferiority margin 0.35

(noninferiority)

Primary Endpoint Visualization Scores -- Study 123/124 --

Score	Efficacy Variables		
	Contrast Enhancement	Border Delineation	Internal Morphology
1	*None*	*None*	*Poorly visible*
2	*Weak*	*Moderate*	*Moderately visible*
3	*Clear*	*Clear but incomplete*	*Sufficiently visible*
4	*Clear and bright*	*Clear and complete*	*N/A*

Primary Endpoint Results

Variable	123			124		
	C + U	U	Δ	C + U	U	Δ
Contrast enhancement	2.26	0.97	1.29 (p<0.001)	2.86	0.93	1.94 (p<0.001)
Border delineation	2.58	1.98	0.60 (p<0.001)	2.94	1.92	1.02 (p<0.001)
Internal morphology	2.58	1.98	0.60 (p<0.001)	2.35	1.57	0.78 (p<0.001)
Avg # lesions detected	8.25	8.08	0.17 *	2.97	2.65	0.32

*** Did not meet noninferiority margin of -0.35**

Outline

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Sources of Safety Data

- 39 Phase 2-4 studies (4549 subjects)
  - Adults (n = 4411), pediatrics (n = 138)
  - Phase 1: 313 healthy volunteers
  - n = 2434 at 0.1 mmol/kg or more
- Global pharmacovigilance
- NSF data

Safety Data
-- Phase 2-4 Trials --

- **Misadministrations (phase 3 trials): 7 / 716**
  - **Double dose**
  - **Resolved with reminder in newsletter**
- **17 SAEs (17 / 4549 ~ 0.4%)**
- **Most SAEs attributed to underlying clinical condition and reflect a CNS process**
- **Investigators considered 1 SAE related to gadobutrol, (crystalluria in pediatric patient)**

Most Frequent Adverse Events

-- Phase 2-4 Trials --

Reaction	Rate (%), n = 4549
Headache	1.5
Nausea	1.2
Injection Site Reaction	0.6
Dysguesia	0.5
Feeling Hot	0.5
Dizziness	0.4
Vomiting	0.4
Rash	0.3
Pruritis	0.2
Erythema	0.2
Dyspnea	0.2
Paresthesia	0.1

Global Pharmacovigilance

- **15 deaths since 1998**
  - **8 anaphylaxis / anaphylactoid shock**
- **AE case reports (thru Sept 2010): 1175; 317 SAEs**
- **“Overdose” reports: 3**
- **Anaphylaxis reported: <1/1000**

NSF

Gadobutrol NSF Reports

Single-agent case reports (Unconfounded), + NSF	**2**
Single-agent case reports (Unconfounded), Not Assessable	**2**
Confounded case reports (subject received >1 GBCA)	**6**

Global NSF Reports, Launch to Feb 2009

GBCA	# NSF reports		# Administrations (millions)
	Single-agent	Confounded	
Omniscan	438	90	47
Optimark	7	11	0.8
Magnevist	135	276	95
MultiHance	0	8	6
Primovist*	0	0	0.15
Vasovist**	0	0	0.05
Gadovist* **	**2**	**8**	**6.0 (Oct. 2010)**
ProHance	1	13	12.3
Dotarem***	1	11	22.4

linear non-ionic
linear ionic,
macrocyclic

* Primovist is Eovist in the U.S.
** Vasovist is Ablavar in the U.S.
*** not marketed in U.S.

EMA/740640/2010

Global Single-agent NSF Reports, -- GBCAs Marketed in U.S. --

GBCA	# Single-agent reports	# Administrations (millions) - global	# Administrations (millions) – U.S.
Omniscan	505	> 49	> 25
Optimark	35	> 3.5	> 2.5
Magnevist	179	> 105	> 50
Multihance	2	> 7.5	> 2.5
Eovist	0	< 0.4	< 0.05
Ablavar	0	< 0.1	0
Prohance*	2	> 15	> 7

contraindicated in hi-risk patients

Source: Dec 2009 AC sponsors' briefing documents

* macrocyclic

Single-agent NSF Case Reports (1 of 2) -- Gadobutrol --

- ***200828599GPV***
  - 68 y.o. M, terminal renal failure, hemodialysis since 2001
  - 61 kg
  - 2005 Apr: 30 ml Gadobutrol (MRA)
  - 2006 Summer: contractures and fibrotic changes of extremities; biopsy inconsistent with NSF
  - 2007 Jun: 10 ml Gadobutrol
  - 2007 Aug: skin biopsy → + NSF
  - Bayer: NSF "not excluded"
  - Cowper Score 4, 2: consistent with NSF

Single-agent NSF Case Reports (2 of 2) -- Gadobutrol --

- ***200923701GPV***
  - 60 y.o. M, chronic renal insufficiency since 2003
  - 90 kg
  - 2008 Jun:
    - 17.5 ml Gadobutrol (MRA)
    - skin rash, musculoskeletal pain, thickened skin on legs
    - skin biopsy → acute NSF
  - 2009 Mar: skin biopsy → chronic NSF
  - Bayer: NSF "not excluded"
  - Cowper Score 3, 4: consistent with NSF

NSF: Submitted Data Support Gadobutrol as a "Lower" Risk Agent

- **Clinical data:**
  - 2 single agent cases in ~6 million administrations
- **Animal studies:**
  - macrocyclic agents less likely to produce NSF-like skin lesions in nephrectomized rats
- **Physico-chemical properties:**
  - macrocyclic (high stability, no measurable Gd^{+3} release)

Sponsor's Proposed Risk Management Plan

- **Labeling:** Detailed dosing chart in the package insert
- **Conspicuous packaging:** Display higher concentration on packaging materials
- **Communication plans:** Make providers aware of key dosing and safety information
- **Educational initiatives:** Stringent training of the field force, web-based programs, and interval feedback

Preliminary Conclusions

- **The clinical efficacy analyses and postmarketing data appear to support gadobutrol approval.**
- **The applicant's proposal to label gadobutrol as a "lower risk" GBCA is supported by the submitted data.**
- **The team acknowledges a need to address ways to minimize the risk for gadobutrol medication error and possible overdose.**

THANK YOU